PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 38/27, 31/56

A1

(11) International Publication Number: **WO 97/46252**

(43) International Publication Date: 11 December 1997 (11.12.97)

(21) International Application Number: PCT/DK97/00239

(22) International Filing Date: 29 May 1997 (29.05.97)

(30) Priority Data:
0623/96 31 May 1996 (31.05.96) DK

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(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: GROWTH HORMONE COMPONENT AND BONE ANTI-RESORPTIVE AGENT IN CYCLIC (COHERENCE) TREATMENT OF OSTEOPOROSIS

(57) Abstract

A novel method of treating or preventing the outbreak of osteoporosis in an animal, e.g. a mammal, in particular a human being, comprises cyclic administration to the individual of a growth hormone component optionally supplemented with continuous administration of a medicament having estrogenic effect and/or a medicament having gestagenic effect.

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GROWTH HORMONE COMPONENT AND BONE ANTI-RESORPTIVE AGENT IN CYCLIC (COHERENCE) TREATMENT OF OSTEOPOROSIS

FIELD OF THE INVENTION

The present invention relates to the treatment or prevention of osteoporosis.

BACKGROUND OF THE INVENTION

Osteoporosis is a metabolic bone disease characterized by an absolute decrease in the bone mass. Clinically this gives rise to an increased susceptibility to fractures. Osteoporosis is a major problem in the developed countries.

The growth of the human skeleton stops by the age of 20-30 years. However, both cortical and trabecular bone is continuously renewed throughout life by the process of remodeling (see e.g. Parfitt, A.M. (1988) in Osteoporosis: Etiology, diagnosis and management; B.L. Riggs, and L.J. Melton III, eds., Raven Press, New York). The remodeling sequence is initiated by osteoblasts or osteoblast-derived cells (bone lining cells) digesting the endosteal membrane, thereby exposing the mineralized bone surface (Chambers, T.J. (1982), J. Cell. Sci., 57, 247-260). Osteoclasts are then recruited from marrow precursors and together with mononuclear cells they resorb a minute amount of bone digging out the resorption lacunae (Eriksen, E.F. et al., J. Bone Min. Res. (1990), 5, 311-319) which is later invaded by osteoblasts refilling the cavity with new bone. In cortical bone, the end product of this process is the Haversian system (osteon) while in the trabecular bone it is seen as a trabecular osteon (Bone Structural Units, BSU or walls). The cells participating in the resorption and formation of one quantum of bone constitute the Bone Multicellular Unit (BMU) (Parfitt, A.M. et al., ibid). In normal subjects, a tight coupling between resorption and formation in both time and space tends to balance the two processes, thereby protecting against bone loss.

The pathogenesis of osteoporosis is still largely unknown. Recent histomorphometric studies (Eriksen, E.F., J. Bone Min. Res. (1990), 5, 311-319), however, have demonstrated a reduced osteoblastic activity in patients suffering from osteoporosis. Eriksen et. al. (Eriksen, E.F. ibid), inv stigated trabecular bone remodeling in 89 osteoporotic women (aged 66 ± 6 years), and found a highly significant reduction in mean wall thickness confirming an earlier report by Darby

and Meunier (Calcif. Tissue Int. (1981), 33, 199-204). This reduction in mean thickness, leads to a pronounced imbalance between resorption and formation not found in subjects not suffering from osteoporosis.

More than 40% of all post-menopausal women suffer low-energy fractures between the age of 50 and 70 years (Jensen, GF et al., Clin. Orthop. (1982), 166, 75-79) and the incidence of osteoporosis in males is increasing (Bengner, U. et al., Calcif. Tissue Int. (1988), 42, 293-296). Treatment with antiresorptive regimens is only able to provide for a 5 to 10% increase of the bone mass. However, as the loss of bone in manifest osteoporosis often amounts from 30 to 50%, an optimal treatment should provide a corresponding increase in the bone mass.

It is a commonly known method to treat menopausal women with estrogen in order to treat or prevent osteoporosis. However, it is also known that administration of high doses of estrogen may increase the risk of developing cancer and does not provide a sufficiently large increase of the bone mass. This has called for preparations comprising moderate amounts of estrogen increasing the demands on the efficiency in the use of the estrogen.

It has been found that osteoblasts have receptors for both growth hormone and insulin growth factors I and II (IGF-I and IGF-II) (Brixen et al., Potential Use of Growth Hormone in the Treatment of Osteoporosis, in Abstracts, Workshop on Growth No. 5, September 25-26, 1992, Moltkes Palace, Copenhagen, Denmark). Although growth hormone has been found to increase bone mass considerably in rats and dogs, it does not seem to significantly affect bone mass in humans.

The object of the present invention is to provide a more efficient method of treating or preventing the development of osteoporosis in humans which may ensure a more efficient use of estrogen in order to increase the bone formation over the level obtainable hitherto.

SUMMARY OF THE INVENTION

The present invention relates, in a first aspect, to the treatment of osteoporosis in an animal and to the use of a growth hormone or a compound having growth hormone like or growth hormone releasing effect as well as somatostatin antagonists (in the following also collectively

referred to in a generic way as the growth hormone component) and a composition with anti-resorptive action on bone (in the following referred to in a generic way as the estrogenic component) in the treatment.

In another aspect, the invention relates to increasing the bone mass and preventing the development of osteoporosis in an animal and to the use of a growth hormone component and an estrogenic component in the treatment.

Further details of the invention will appear from the appended claims.

DETAILED DESCRIPTION OF THE INVENTION

It has surprisingly been found that when a growth hormone, somatostatin antagonist, or a growth hormone secretagogue (growth hormone component) is administered cyclically and, simultaneously, a composition with anti-resorptive action on bone is administered continuously to an animal, loss of the bone mass is stopped and an increase of bone mass is seen.

The present invention relates to a method of treating as well as a method of preventing the development of osteoporosis and related disorders such as osteopenia in an animal comprising simultaneous administration to the animal of amounts of a growth hormone component and an estrogen component effective, in combination, to increase the bone mass in the animal.

The term "animal" used in the present context includes, but is not limited to birds, such as chicken, ducks or turkeys, fish such as salmon, trout or tuna, and mammals such as cows, horses, sheep and human beings. The animal to be treated is preferably a mammal and more preferred a human being, most preferably a woman, and the growth hormone is preferably human growth hormone.

The term "simultaneous" used in connection with administration of the growth hormone component and the estrogen component in the present context is meant to designate administration of the two drugs in such a manner that, any time, both of them ar available in adequate amounts to provid the benefit of the invention. This does not imply that both drugs must be administered at exactly the same time as *e.g.* by precisely simultaneous injection of

the two drugs, but rather that both drugs are intended to be giv n in any practical manner which provides for optimal availability thereof.

As indicated above, it has turned out that, optimally, the growth hormone component is administered in a cyclic way which means that periods in which growth hormone component is administered alternate with periods where no growth hormone component is administered as further specified in the present text. The estrogen component is preferably administered daily.

One of the drugs may be administered by injection and the other may given orally, e.g. in the form of a tablet. Alternatively, it is envisaged that each medicament may, individually, be administered by injection, in the form of a patch for topical application, by nasal administration or in the form of a tablet. Presently however, growth hormone is preferably administered by injection. It could also be envisaged that growth hormone was used in a sustained release formulation.

According to a preferred aspect of the invention, the estrogen is given continuously during the period of treatment whereas the growth hormone is given at intervals. A preferred method of administration comprises daily administration of estrogen and periodical administration of growth hormone for a period of from about 2 days to about 28 days, preferably from about 2 days to about 14 days, more preferred from about 3 days to about 10 days, in particular from about 3 days to about 7 days, with intervals of from about 1 week to about 26 weeks, preferably from about 3 weeks to about 26 weeks, more preferably from about 6 to about 12 weeks, even more preferred from about 6 weeks to about 10 weeks, in particular about 8 weeks, between the periods in which of growth hormone is administered. The estrogen component is administered in the amount from 0.001 mg to 10 mg/kg body weight/day. When the estrogen component used is estradiol, the total amount given per day is from about 0.5 mg to about 4 mg, preferably from about 1 mg to about 2 mg. If another estrogen is used, an amount which has an equivalent anti-resorptive effect on bone is given. When a gestagen is included in the regimen, this can be norethisterone acetate which is administered in an amount of from about 0.1 mg to about 2.0 mg, preferably from about 0.25 mg to about 2.0 mg per day according to the schedule. If another estrogen is used, an equivalent amount is given.

In the present context, "estrog n" is considered to encompass any preparation containing an estrogenic substance such as a natural human estrogen such as estrone, 17-β-estradiol and

estradiol or d rivatives thereof being cleaved *in vivo* to form natural estrogens, natural equine estrogens prepared from urine from horses, or artificial estrogens without steroid structure such as dienestrol. The "estrogen" could also be selected from the group of non-steroidal estrogen directed therapeutics (NSERTs) such as Centchroman, Levormeloxifene, Raloxifene, Droloxifene, Tamoxifene, Idoxifene, or the like or structurally related compounds thereof, such as e.g the compounds disclosed in WO 96/21656, WO 95/10513, US Patent 5,280,040, WO 96/09040, EP 0693488, WO 95/34557, EP 0617030, WO 93/10741, US Patent 5,254,568, EP 0683170, EP 0659413, EP 0652006, EP 0652007 and EP 0674903, the contents of which are hereby incorporated by reference. As "estrogen" may be used a composition containing an estrogenic compound as the only pharmacologically active component or a composition which further to the estrogenic agent also contains a gestagen.

In the present context, "growth hormone" may be growth hormone of any origin such as avian, bovine, equine, human, ovine, porcine, salmon, trout or tuna growth hormone, preferably bovine, human or porcine growth hormone, human growth hormone being most preferred. The growth hormone used in accordance with the invention may be native growth hormone isolated from a natural source, e.g. by extracting pituitary glands in a conventional manner, or a growth hormone produced by recombinant techniques, e.g. as described in E.B. Jensen and S. Carlsen in Biotech and Bioeng. 36, 1-11 (1990). The growth hormone may also be a truncated form of growth hormone wherein one or more amino acid residues has (have) been deleted; an analogue thereof wherein one or more amino acid residues in the native molecule has (have) been substituted by another amino acid residue, preferably a natural amino acid residue, as long as the substitution does not have any adverse effect such as antigenicity or essentially reduced activity; or a derivative thereof, *e.g.* having an N- or C-terminal extension such as Met-hGH. The preferred growth hormone is human growth hormone (hGH).

Compounds having growth hormone like or growth hormone releasing effect may e.g. be growth hormone releasing hormone (GHRH), growth hormone releasing factor or smaller oligo or polypeptides stimulating the release of growth hormone in vivo such as short-chain growth hormone releasing peptides, or growth factors such as IGF-I or IGF-II, as well as somatostatin antagonists. Examples of suitable growth hormone components are growth hormone (GH), IGF-I, IGF-II, PACAP, GHRH, truncated GHRH, GHRP-1, GHRP-2, GHRP-6, MK-677 disclosed in R.P. Margund et al., PNAS 92(15), 1995, p. 7001, hexarelin disclosed in WO

91/18016, as well as compounds disclosed in WO 95/17422, WO 95/17423, WO 96/05195, WO 96/22997, WO 96/24580, WO 96/24587, WO 97/00894, such compounds are e.g.

H-Hisψ(CH_2NH)D-Trp-Ala-Trp-D-Phe-Lys-NH_2,

H-His-D-Trpψ(CH_2NH)Ala-Trp-D-Phe-Lys-NH_2,

H-His-D-Trp-Alaψ(CH_2NH)Trp-D-Phe-Lys-NH_2,

H-His-D-Trp-Ala-Trpψ(CH_2NH)D-Phe-Lys-NH_2,

H-His-D-Trp-Ala-Trp-D-Pheψ(CH_2NH)Lys-NH_2,

H-D-Ala-D-2Nal-Alaψ(CH_2NH)Trp-D-Phe-Lys-NH_2,

H-D-Ala-D-2Nal-Ala-Trp-D-Pheψ(CH_2NH)Lys-NH_2,

(3-(4-Imidazolyl)propionyl)-D-2Nal-Ala-Trp-D-Pheψ(CH_2NH)Lys-OH,

(3-(4-Imidazolyl)propionyl)-D-2Nal-Ala-Trp-D-Pheψ(CH_2NH)Lys-NH_2,

(3-(4-Imidazolyl)acryloyl)-D-2Nal-Ala-Trp-D-Pheψ(CH2NH)Lys-NH2,

H-D-Ala-D-Phe-Ala-Trp-D-Pheψ(CH_2NH)Lys-NH_2,

(2R)-(H-D-Ala-D-Phe-Ala-Trp-NH)-3-phenylpropylamine,

(2S)-(H-D-Ala-D-2Nal-Alaψ(CH_2NH)Trp-D-Phe-NH)-6-aminohexanol,

H-D-Ala-D-2Nal-Alaψ(CH_2NH)Trp-D-Phe-NH_2,

4-(H-D-Ala-D-2Nal-Alaψ(CH_2NH)Trp-D-Phe-NH)butylamine,

(2R)-(H-D-Ala-D-2Nal-Ala-Trp-NH)-3-phenylpropylamine,

((2R)-(H-D-Ala-D-2Nal-Ala-Trp-NH)-3-phenylpropylamino)hexylamine,

(2R)-(H-D-2Nal-Ala-N-Bzl-Gly-NH)-3-phenylpropylamine,

(2R)-(H-D-Ala-D-2Nal-Ala-N-Bzl-Gly-NH)-3-phenylpropylamine,

H-Aib-D-2Nal-Ala-N-Bzl-Gly-D-Pheψ(CH_2NH)Lys-NH_2,

(2S)-((3-(4-Imidazolyl)propionyl)ψ(CH_2NH)D-Phe-Ala-Trp-D-Phe-NH)-6-aminohexanol,

(2S)-((3-(4-Imidazolyl)propionyl)-D-Pheψ(CH_2NH)Ala-Trp-D-Phe-NH)-6-aminohexanol,

(2S)-((3-(4-Imidazolyl)propionyl)-D-Phe-Alaψ(CH_2NH)Trp-D-Phe-NH)-6-aminohexanol,

(2S)-((3-(4-Imidazolyl)propionyl)-D-Phe-Ala-Trpψ(CH_2NH)D-Phe-NH)-6-aminohexanol,

(2S)-(2R)-((3-(4-Imidazolyl)propionyl)-D-Phe-Ala-Trp-NH)-3-phenylpropylamino)-6-aminohexanol,

3-((3-(4-Imidazolyl)propionyl)-D-Trp-Ala-ψ(CH_2NH)Trp-D-Phe-NH)propylamine,

(2S)-((3-(4-Imidazolyl)propionyl)-D-Phe-Ala-Trp-D-Pheψ(CH_2NH)NH)-6-aminohexanol,

(2S)-((3-(4-Imidazolyl)propionyl)-D-Trp-Alaψ(CH_2NH)Trp-D-Phe-NH)-6-aminohexanol,

3-((3-(4-Imidazolyl)propionyl)-D-Trp-Alaψ(CH_2NH)Trp-D-Phe-NH)propylamine,

H-D-Ala-D-2Nal-Ala-N-Bzl-Gly-D-Pheψ(CH_2NH)Lys-NH_2,

H-Aib-D-2Nal-Ala-N-Bzl-Gly-D-Pheψ(CH_2NH_2),

H-Ala-Hisψ(CH_2NH)D-2Nal-D-Phe-Lys-NH_2,

H-Ala-Ala-D-2Nal-D-Phe-Lys-NH_2,

H-His-D-2Nal-D-Phe-Lys-NH_2,

(3-(4-Imidazolyl)propionyl)-D-2Nal-D-Phe-Lys-NH_2,

H-D-Lys-D-2Nal-D-Phe-Lys-NH_2,

H-5Apent-His-D-2Nal-D-Phe-Lys-NH_2,

H-D-Ala-D-2Nal-D-Phe-Lys-NH_2,

H-5Apent-D-2Nal-D-Phe-Lys-NH_2,

(n-Propyl)-His-D-2Nal-D-Phe-Lys-NH_2,

H-Ala-3Pyal-D-2Nal-D-Phe-Lys-NH_2,

H-Ala-Phe(4-NH_2)-D-2Nal-D-Phe-Lys-NH_2,

H-D-Ala-His-D-2Nal-D-Phe-Lys-NH_2,

(2-(4-Imidazolyl)acetyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-(4-Imidazolyl)acryloyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethyl benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminophenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,

(4-Aminophenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminocrotonoyl)-D-2Nal-D-Phe-Lys-NH_2,

(4-Piperidino-carboxyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-NH_2,

(H-Ala-His-D-2Nal-D-Phe-NH)hexane,

6-(H-Ala-His-D-2Nal-D-Phe-NH)hexylamine,

5-(H-Ala-His-D-2Nal-D-Phe-NH)pentylanaine,

H-Ala-His-D-2Nal-D-Pheψ(CH_2NH)Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-Lys-OH,

(2S)-(H-Ala-His-D-2Nal-D-Phe-NH)-6-aminohexanol,

(2-(H-Ala-His-D-2Nal-D-Phe-NH)ethyl)benzene,

2-(H-Ala-His-D-2Nal-D-Phe-NH)ethylamine,

4-((H-Ala-His-D-2Nal-D-Phe-NH)methyl)benzylamine,

H-Ala-His-D-2Nal-D-Phe-Lys(maltosyl)-NH_2,

H-Ala-His-D-2Nal-D-Phe-Phe-NH_2,

H-Ala-His-D-2Nal-D-Phe-D-Phe-NH_2,

H-Ala-His-D-Phe-D-Phe-Lys-NH_2,

H-Ala-His-D-Trp-D-Phe-Lys-NH_2,

H-His-D-2Nal-D-Trp-Lys-NH_2,

H-Ala-His-D-1Nal-D-Phe-Lys-NH_2,

H-Ala-Phe-D-2Nal-D-Phe-Lys-NH_2,

H-Ala-His-D-2Nal-D-Phe-Lys(maltosyl)-NH_2,

(2R)-(H-Ala-His-D-2Nal-D-Phe-Lys-NH)-3-phenylpropylamine,

H-Ala-N-Me-(2-aminobenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-(Methylaminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(4-(Aminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

H-His-Ala-D-2Nal-D-Phe-Lys-NH_2,

4-(H-Ala-His-D-2Nal-D-Phe-NH)butylamine,

3-(H-Ala-His-D-2Nal-D-Phe-NH)propylamine,

(3-(Dimethylaminomethyl)benzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Amino-3-methylbutanoyl)-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-hPhe-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)y(CH_2NH)D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-hPhe-Lys-NH_2,

(3-Amino-3-methylbutanoyl)-His-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-Bzl-Gly-Lys-NH_2,

(2S)-(3-aminomethylbenzoyl)y(CH_2NH)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(2S)-((3-aminomethylbenzoyl)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(3-Aminomethylbenzoyl)-D-2Nal-D-Thial-Lys-NH_2,

(2S)-(H-Aib-Hisψ(CH_2NH)-D-2Nal-D-Phe-NH)-6-aminohexanol,

(3-Aminomethylbenzoyl)-D-2Nal-D-3Pyal-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe(4-F)-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe(4-OMe)-Lys-NH_2,

(2-Aminomethylphenylacetyl)-D-2Nal-D-Phe-Lys-NH_2,

(2-Aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(4-pyridyl)ethane,

H-Aib-Phe-D-2Nal-D-Phe-Lys-NH_2,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(H-Aib-His-D-2Nal-D-Phe-NH)-(4-pyridyl)ethane,

H-Aib-Hisψ(CH_2NH)-D-2Nal-D-Phe-Lys-OH,

(3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Gly-NH_2,

H-Aib-His-D-2Nal-D-Phe-Ala-NH_2,

H-Aib-His-D-2Nal-D-Phe-Orn-NH_2

(5-Aminomethylthienyl-2-carbonyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-D-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Dab-NH_2,

H-Aib-His-D-2Nal-D-Pheψ(CH_2NH)-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-N-Me-Lys-NH_2,

(3-Aminomethylthienyl-2-carbonyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phe-Lys-N$(Me)_2$,

(3R)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3S)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-1Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Trp-Lys-NH_2,

(Furfuryl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

(2-Pyridylmethyl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-(3-aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-3Pyal-D-2Nal-D-Phe-Lys-NH_2,

(3S)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(3R)-Piperidinecarbonyl-D-2Nal-D-Phe-Lys-NH_2,

(2-(H-Aib-His-D-2Nal-NH)ethyl)benzene,

N,N-di(2R-Hydroxypropyl)-(3-aminomethylbenzoyl)-D-2Nal-D-Phe-Lys-NH_2,

(2R-Hydroxypropyl)-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Pheψ(CH_2NH)Lys-NH_2,

(3-Aminomethylbenzoyl)-N-Me-D-2Nal-D-Phe-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-D-Phe-N-Me-Lys-NH_2,

H-D-Thr-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

(3-Aminomethylbenzoyl)-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

H-Hyp-His-D-2Nal-D-Phe-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-(phenethyl)-Gly-Lys-NH_2,

H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

H-Aib-His-D-2Nal-D-Phey($CH_2N(Me)$)Lys-NH_2,

3-(H-Aib-His-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

2-(H-Aib-His-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

(3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,

3-((Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

2-(H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)-ethane,

3-(H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

3-((3R)-Piperidinecarbonyl-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

3-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)morpholinopropane,

H-Aib-His-D-2Nal-N-Me-D-Phe-Hyp-NH_2,

2-((3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

2-((3R)Piperidinecarbonyl-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane,

H-Aib-His-D-2Nal-D-Phe-Lys-NH_2,

3-Amino-3-methyl-N-(4-oxo-5-(2'-(tetrazol-5-yl)biphenyl-4-ylmethyl)-2,3,4,5-tetrahydro-1H-naphtho[2,1-b]azepin-3-yl)butyramide,

3-Amino-3-methyl-N-(4-oxo-5-(4-(4-(5-methyl-[1,3,4]oxadiazol-2-yl)-thien-3-yl)benzyl)-2,3,4,5-tetrahydro-lH-naphtho-[2,1-b]azepin-3-yl)butyramide,

3-((2R)-Hydroxypropylamino)-3-methyl-N-(5-(4-(4-(5-methyl-[1,3,4]oxadiazol-2-yl)thien-3-yl)benzyl)-4-oxo-2,3,4,5-tetrahydro-1H-naphtho[2,1-b]azepin-3-yl)butyramide,

1-Aminocyclopropanecarboxylic acid (4-oxo-5-(2'-(1H-tetrazole-5-yl)-biphenyl-4-ylmethyl)-2,3,4,5-tetrahydro-1H-naptho[2,1-b]azepin-3-yl)amide,

3-Amino-3-methyl-N-(5-benzyl-4-oxo-2,3,4,5-tetrahydro-1H-naptho[2,1-b]azepin-3-yl)butyramide,

(3R) Piperidine-3-carboxylic acid ((1R,2E)-4-hydroxymethyl-1-(2-naphthyl)methyl-5-phenylpent-2-enyl)amide,

3-Aminomethyl-N-((1R,2E)-4-hydroxymethyl-1-(2-naphthyl)methyl-5-phenylpent-2-enyl)-benzamide,

Piperidine-4-carboxylic acid (1-{[1-(3-carbamoyl-[1,2,4]oxadiazol-5-yl)-2-(2-naphthyl)ethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl) amide,

5-{(1R)-1-[(2R)-2-(Piperidine-4-carbonylamino)-3-(2-naphthyl)propionyl-N-m thylamino]-2-(2-naphthyl)ethyl}-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester,

5-{1-[2-(3-Aminomethylbenzoyl)-3-(2-naphthyl)propionyl-N-methylamino]-2-(2-naphthyl)ethyl}-[1,2,4]oxadiazol-3-carboxylic acid ethyl ester,

5-{(1R)-1-[(2R)-2-(3-Aminomethylbenzoylamino)-3-(2-naphthyl)propionylamino]-2-phenylethyl}-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester, or the triflouroacetic acid salt thereof;

Piperidine 4-carboxylic acid [(1R)-1-{(1R)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-2-phenylethylcarbamoyl}-2-(2-naphthyl)ethyl]amide,

3-Aminomethyl-N-[(1R)-1-{(1R)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-2-phenylethylcarbamoyl}-2-(2-naphthyl)ethyl]benzamide,

4-Amino-4-methyl-pent-2-enoic acid [(1R)-1-{(1R)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-2-phenylethylcarbamoyl}-2-(2-naphthyl)ethyl]amide,

(3R)-Piperidine 3-carboxylic acid [(1R)-1-((1R)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-2-phenylethylcarbamoyl)-2-(2-naphthyl)ethyl]amide,

3-Aminomethyl-N-((1R, 2E, 4S)-4-carbamoyl-5-(2-naphthyl)-1-(2-naphthyl)methylpent-2-enyl)benzamide,

Piperidine-4-carboxylic acid ((1R,2E,4S)-4-carbamoyl-5-(2-naphthyl)-1-(2-naphthyl)methylpent-2-enyl) amide,

N-((1R)-1-(((1R)-1-(((1S)-5-Amino-1-(dimethylcarbamoyl)pentylcarbamoyl)-2-phenylethoxy)-methyl)-2-(2-naphthyl)ethyl)-3-aminomethylbenzamide,

N-((1R,4S)-4-(((1S)-5-Amino-1-(dimethylcarbamoyl)pentyl)carbamoyl)-1-((2-naphthyl)methyl)-2-oxo-5-phenylpentyl)-3-aminomethylbenzamide,

N-((1R,2R,4S)-4-(((1S)-5-Amino-1-(dimethylcarbamoyl)pentyl)carbamoyl)-2-hydroxy-1-(2-naphthyl)methyl-5-phenylpentyl)-3-aminomethylbenzamide,

Piperidine-3-carboxylic acid ((1R, 2R, 4S)-4-(((1S)-5-amino-1-(dimethylcarbamoyl)pentyl)-carbamoyl)-2-hydroxy-1-((2-naphthyl)methyl)-5-phenylpentyl) amide,

5-((1R)-1-(N-Methyl-N-((2R)-3-(2-naphthyl)-2-(piperidin-4-yl-carbonylamino)propionyl)amino)-2-(2-naphthyl)ethyl)-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester,

5-((1R)-1-(N-((2R)-2-(3-Aminomethylbenzoylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-2-(2-naphthyl)ethyl)-[1,2,4]oxadiazole-3-carboxylic acid ethyl ester,

5-((1R)-1-(N-((2R)-2-(3-Aminomethylbenzoylamino)-3-(2-naphthyl)propionyl)-N-methylamino)-2-phenylethyl)-[1,3,4]oxadiazole-2-carboxylic acid amide,

(2E)-5-Amino-5-methylhex-2-enoic acid {(1R)-1-[N-methyl-N-((1R)-1-(3-methyl-[1,2,4]-oxadiazol-5-yl)-2-(2-naphthyl)-ethyl)carbamoyl]-2-(2-naphthyl)ethyl} amide,

4-Amino-4-methylpent-2-enoic acid N-[(1R)-1-{N-methyl-N-[(1R)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-2-(2-naphthyl)ethyl]carbamoyl}-2-(2-naphthyl)ethyl]-N-methylamide,

4-Amino-4-methylpent-2-enoic acid [(1R)-1-{N-methyl-N-[(1R)-1-(3-methyl-[1,2,4]oxadiazol-5-yl)-2-(2-naphthyl)ethyl]carbamoyl}-2-(2-naphthyl)ethyl]amide,

3-Aminomethyl-N-((1R)-1-{N-[(1R)-1-(((dimethylcarbamoyl)methoxy)methyl)-2-phenylethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)-N-methylbenzamide,

5-((1R)-1-(((2R)-2-(((4E)-4-Amino-4-methylpent-2-enoyl)methylamino)-3-(2-naphthyl)-propionyl)methylamino)-2-phenylethyl)-[1,3,4]-oxadiazole-2-carboxylic acid amide,

Piperidine-4-carboxylic acid N-methyl-N-{-1([methyl-1-(3-methyl-[1,2,4]oxadiazole-5-yl)-2-(2-naphthyl)ethylcarbamoyl)-2-(2-naphthyl)ethyl}amide,

Piperidine-4-carboxylic acid N-{-1([methyl-1-(3-methyl-[1,2,4]-oxadiazole-5-yl)-2-(2-naphthyl)ethylcarbamoyl)-2-(2-naphthyl)ethyl}amide,

5-{1-[2-(piperidine-4-carbonylamino)-3-(2-naphthyl)propionyl-N-methylamino]-2-(2-naphthyl)ethyl}-[1,2,4]oxadiazole-3-carboxylic acid 2-propyl ester,

5-{1-[2-(piperidine-4-carbonylamino)-3-(2-naphthyl)propionyl-N-methylamino]-2-(2-naphthyl)ethyl}-[1,2,4]oxadiazole-3-carboxylic acid, trifluoro acetate,

Piperidine-4-carboxylic acid (1-{[1-(3-methylcarbamoyl-[1,2,4]oxadiazol-5-yl)-2-(2-naphthyl)-ethyl]-N-methylcarbamoyl}-2-(2-naphthyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid {1-[N-(1-(3-benzylcarbamoyl-[1,2,4]oxadiazol-5-yl)-2-phenylethyl)-N-methyl-carbamoyl]-2-(2-naphthyl)ethyl} amide,

(2E)-5-Amino-5-methylhex-2-enoic acid N-{(1R)-1-[((1R)-1-benzyl-2,5-dihydroxypentyl)-N-methylcarbamoyl]-2-(2-naphthyl)ethyl}-N-methylamide,

3-Aminomethyl-N-((1R)-1-{N-[(1R)-1-(2-hydroxyethoxymethyl)-2-phenylethyl]-N-methyl-carbamoyl}-2-(2-naphthyl)ethyl)-N-methylbenzamide,

Piperidine-4-carboxylic acid ((1R,2E)4-hydroxymethyl-5-(2-naph-thyl)-1-((2-naphthyl)methyl)-pent-2-enyl)amide,

Piperidine-4-carboxylic acid ((1R)-2-(2-naphthyl)-1-((1R)-2-(2-naphthyl)-1-(1-phenethyl-1H-tetrazol-5-yl)ethyl-carbamoyl)ethyl)amide,

Piperidine-4-carboxylic acid N-methyl-N-((1R9-2-(2-naphthyl)-1-((1R)2-(2-naphthyl)-1-thio-carbamoylethylcarbamoyl)ethyl)amide,

Piperidine-4-carboxylic acid ((1R)-1-((1R)-1-(4-carbamoyl-5-phe-nyl-1,3-thiazol-2-yl)-2-(2-naphthyl)ethylcarbamoyl)-2-(2-naphthyl)ethyl)amide,

(2E)-5-Amino-5-methylhex-2-enoic acid {1-[N-(1-(3-methylcarbamoyl-[1,2,4]oxadiazol-5-yl)-2-phenylethyl)-N-methyl-carbamoyl]-2-(2-naphthyl)ethyl} amide,

(2E)-5-Amino-5-methylhex-2-enoic acid {1-[N-(1-(3-dimethylcarbamoyl-[1,2,4]oxadiazol-5-yl)-2-phenylethyl)-N-methyl-carbamoyl]-2-(2-naphthyl)ethyl} amide,

(2E)-5-Amino-5-methyl-N-((1R)-1-(N-((1R)-1-(2-hydroxyethoxymethyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylhex-2-enoic acid amide,

(2E)-5-Amino-5-methyl-N-((1R)-1-(N-((1R)-1-(2-hydroxy-2-methylpropoxymethyl)-2-phenylethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylhex-2-enoic acid,

1-Benzyl-3-(3-(morpholin-4-yl)propyl)-1-(naphth-2-yl)methyl-thiourea, or the hydrchloride salt thereof;

1-Benzyl-3-(3-dimethylaminopropyl)-1-phenyl-thiourea, or the hydrochloride salt thereof;

2-[3-(3-(Morpholin-4-yl)propyl)-1-(naphth-2-yl)methyl-thioureido]-3-phenyl-propionamide,

N-(4-Aminobutyl)-2-[3-((3-amino-3-methyl)butyl)-1-(naphth-2-yl)methyl-thioureido]-3-phenyl-propionamide,

N-(4-Aminobutyl)-2-(N-(naphth-2-yl)methyl-N'-(piperidin-3-yl)methyl-guanidino)-3-phenyl-propionamidë,

N-(4-Aminobutyl)-2-[1-methyl-3-(naphth-2-yl)methyl-3-(2-(piperidin-2-yl)ethyl)-thioureido]-3-(naphth-2-yl)propionamide,

3-(3-(Morpholin-4-yl)propyl)-1-(naphth-2-yl)methyl-1-[2'-(1H-tetrazol-5-yl)-biphenyl-4-ylmethyl]-thiourea, or the hydrochloride salt thereof;

N-((1-Carbamoyl-2-phenyl)ethyl-N-methyl-2-[3-((3-morpholin-4-yl)propyl)- thioureido]-3-(naphth-2-yl)propionamide,

3-(3-(Dimethylamino)propyl)-1-(naphth-1-yl)methyl-1-phenylthiourea, or the hydrochloride salt thereof;

1-Benzyl-3-(3-(morpholin-4-yl)propyl)-1-phenylthiourea,

1,1-Dibenzyl-3-(3-(morpholin-4-yl)propyl)thiourea, or the hydrochloride salt thereof;

1-Benzyl-3-(3-(dimethylamino)propyl)-1-((naphth-2-yl)methyl)thiourea, or the hydrochloride salt thereof;

1-Benzyl-3-(3-(morpholin-4-yl)propyl)-1-(pheneth-2-yl)thiourea, or the hydrochloride salt thereof;

1-Benzyl-3-(3-(morpholin-4-yl)propyl)-1-(quinolin-3-yl)thiourea, or the dihydrochloride salt th reof;

1-Benzyl-3-(3-(morpholin-4-yl)propyl)-1-(pyridin-2-yl)thiourea, or the hydrochloride salt thereof;

1-Benzyl-3-(3-(morpholin-4-yl)propyl)-1-(4-methoxyphenyl)thiourea, or the hydrochloride salt thereof;

1-Benzyl-3-(3-(morpholin-4-yl)propyl)-1-(4-([1,2,3]thiadiazol-4-yl)benzyl)thiourea, or the hydrochloride salt thereof; or

3-(3-Dimethylaminopropyl)-1-((naphth-2-yl)methyl)-1-phenylthiourea, or the hydrochloride salt thereof;

2-Phenyl-3,4-dihydro-2H-quinoline-1-carbothioic acid (3-(dimethylamino) propyl) amide, or the hydrochloride salt thereof;

Benzyl-3,4-dihydro-2H-quinoline-1-carbothioic acid (3-(dimethylamino)propyl)amide,

1-(3-((Morpholin-4-yl)propyl)thiocarbamoyl)-1,2,3,4-tetrahydro-1H-quinoline-2-carboxylic acid N-(1-carbamoyl-2-(napht-1-yl)ethyl)-N-methylamide,

2-(3-((Morpholin-4-yl)propyl)thiocarbamoyl)-1,2,3,4-tetrahydro-1H-isoquinoline-3-carboxylic acid N-[1-((4-aminobutyl)carbamoyl)-2-(naphth-1-yl)ethyl]-N-methylamide; or

2-Phenyl-3,4-dihydro-2H-quinoline-1-carbothioic acid (3-(morpholin-4-yl)propyl) amide, or the hydrochloride salt thereof;

(R)-2-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me)-3-phenylpropanol, or the TFA salt thereof;

3-((3-Aminomethylbenzoyl))N-Me-D-2Nal-N-Me-D-Phe-NH)-1-1N,N-dimethylaminopropane, or the TFA salt thereof;

3-(((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-1-N,N-dimethylaminopropane, or the TFA salt thereof;

2-(((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-(1-methyl-2-pyrrolidinyl)ethane, or the TFA salt thereof;

H-Aib-His-D-2Nal-N-Me-D-Phe-Ser-NH_2, or the TFA salt thereof;

(3-Aminomethylbenzoyl)-D-2Nal-N-Me-D-Phe-Lys-NH_2, or the TFA salt thereof;

(4-Piperidinecarbonyl)-D-2Nal-N-Me-D-Phe-NH_2, or the TFA salt thereof;

((3R)-3-Piperidinecarbonyl)-D-2Nal-N-Me-D-Phe-NH_2, or the TFA salt thereof;

(3-Aminomethylbenzoyl)-D-Phe-N-Me-D-Phe-NH_2, or the TFA salt thereof;

(3-Aminomethylbenzoyl)-N-Me-D-Phe-N-Me-D-Phe-Lys-NH_2, or the TFA salt thereof;

((3R)-3-Piperidinecarbonyl)-N-Me-D-Phe-N-Me-D-Phe-Lys-NH_2, or the TFA salt thereof;

H-Aib-His-N-Me-D-Phe-N-Me-D-Phe-Lys-NH_2, or the TFA salt thereof;

((3R)-3-Piperidinecarbonyl)-N-Me-D-2Nal-N-Me-D-Phe-NH_2, or the TFA salt thereof;

(2R)-2-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me)-3-(2-naphthyl)propanol, or the TFA salt thereof;

(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH_2, or the TFA salt thereof;

3-((3-Aminomethylbenzoyl)-N-Me-D-Phe-NH)-1-N,N-dimethylaminopropane,
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH_2, or the TFA salt thereof;
(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-Lys-NH_2,
H-Aib-Ala-D-2Nal-N-Me-D-Phe-Lys-NH_2, or the TFA salt thereof;
H-Aib-His-D-2Nal-N-Me-D-Phe-NH_2, or the TFA salt thereof;
2-((3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-1-morpholinoethane,
(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH-Me,
3-((3-Methylaminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-NH)-1-N,N-dimethyl-aminopropane,
(3-Aminomethylbenzoyl)-N-Me-D-2Nal-N-Me-D-Phe-N-Me_2,
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NH_2,
3-Aminomethylbenzoyl-N-Me-D-2Nal-N-Me-D-Phe-NH-CH_3, or the TFA salt thereof;
3-methylaminomethylbenzoyl-N-Me-D-2Nal-N-Me-D-Phe-NH-CH_3, or the TFA salt thereof;
H-Aib-His-N-Me-D-2Nal-N-Me-D-Phe-NHMe, or the HCl salt thereof;
and Piperidine-4-carboxylic acid-N-((1R)-1-(N-((1R)-2-(4-iodophenyl)-1-(methylcarbamoyl)ethyl)-N-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide,
(2E) 5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methyl-carbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide, or the hydrochloride salt thereof;
(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(((1R)-1-((2S)-2-hydroxypropylcarbamoyl)-2-phenylethyl)-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide, or
(2E)-5-Amino-5-methylhex-2-enoic acid ((1R)-1-(((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide.

Other examples of suitable growth hormone secretagogues are compounds disclosed in WO 94/13696, WO 94/19367, WO 95/14666, WO 94/11012, WO 96/15148, WO 95/34311, WO 95/13069, WO 93/04081 and WO 97/07117, the contents of which are hereby incorporated by reference.

For the purpose of the present invention, the expression "increase the bone mass" is used to designate a condition wherein the balance between the resorption and formation of bone is shifted towards the formation so as to at least stop the loss of bone mass.

A proposed dosage regimen for treating post-menopausal human beings having manifest osteoporosis, which may e.g. be a spinal osteoporosis and a compression fracture of at least one vertebra or a manifest bone mineral density in lumbar spine of femoral neck, may e.g. be treatment with one tablet of Kliogest® (Novo Nordisk A/S, Bagsvaerd, Denmark; each tablet of Kliogest® comprises 2 mg of estradiol and 1 mg of norethisteron acetate) per day for two years and daily injections s.c. of 0.01-1 IU per kg body weight per day, preferably 0.1-0.2 IU per kg body weight per day, more preferably 0.2 IU per kg body weight per day (the specific activity of GH is 3 IU/mg), of Norditropin® biosynthetic human growth hormone (B-hGH, Novo Nordisk A/S, Bagsvaerd, Denmark), a somatostatin antagonist or GH secretagogue or a growth hormone component which can release the set amount of GH for a period of from about 2 days to about 28 days, preferably from about 2 days to about 14 days, more preferred from about 3 days to about 10 days, in particular from about 3 days to about 7 days, with intervals of from about 1 week to about 26 weeks, preferably from about 3 weeks to about 26 weeks, more preferably from about 6 weeks to about 12 weeks, more preferred from about 6 weeks to about 10 weeks, in particular about 8 weeks, between the periods in which of growth hormone is administered. The injections may be carried out using a normal syringe or using a pen device such as a Nordiject® pen device (Novo Nordisk A/S, Bagsvaerd, Denmark). The estrogen is preferably a preparation comprising a combination of an estrogen and a gestagen. For women who have no uterus, it is preferred to give an estrogen alone.

According to another aspect of the invention, human growth hormone is used for the manufacture of a medicament for treating osteoporosis by simultaneous administration together with estrogen.

According to yet another aspect of the invention, human growth hormone is used for the manufacture of a medicament for preventing the development of osteoporosis by simultaneous administration together with estrogen.

The invention is further illustrated in the following example which is not in any way intended to limit the scope of the invention as claimed.

EXAMPLE 1:

An approximately 62-year old postmenopausal woman with manifest osteoporosis was treated for one year with Kliogest® tablets orally every day and Norditropin® growth hormone subcutaneously for seven days every 8th week. Every day without interruption, one Kliogest® tablet was given. In the seven-day periods when Norditropin® was administered, the dosage used was 0.2 IU/kg body weight/day. The osteoporosis was radiologically verified. The woman did not suffer from any other bone disease than osteoporosis. She had normal glucose metabolism and was not familiarly disposed to non-insulin dependent diabetes mellitus. She did not abuse alcohol or drugs and had no vaginal bleedings of unknown aetiology, and had never suffered thromboembolic disorders during estrogen treatment.

Bone mineral density of the lumbar spine (L2-L4), and of the femoral neck was assessed by quantitative digital radiography before the therapy started and after six and twelve months of therapy. Bone mineral density at the spine increased by 3% and 15% after six and twelve months of therapy, respectively, compared to baseline. In g/cm^2 bone mineral density of lumbar spine had increased from 0.611 to 0.631 and 0.703, respectively after six and twelve months of combined estrogen and growth hormone therapy.

Bone mineral density of the femoral neck increased by 11.4% after twelve month of therapy compared to baseline. In g/cm^2 bone mineral density of the femoral neck had increased from 0.688 to 0.774.

EXAMPLE 2:

A randomized double-blind placebo controlled study with four arms in 57 women (aged 45-75 years) with post-menopausal osteoporosis (BMD > 2SD below mean, and one spinal fracture(s) and/or colles fracture(s)), has been performed.

Four arms design:

GH + Kliogest®

GH + Placebo

Placebo + Kliogest®

Placebo + Placebo.

Kliogest® was administered daily in an oral form for 12 months. GH was injected s.c. in the evening for 7 days very 2 months during the 12 months treatment period in a dose of 0.2 IU/mg/day.

The results in percentage change in BMD after 12 months treatment showed that the effect n BMD spine was greater in patients receiving the combined treatment of Kliogest® and GH, mean percent increase 9.5%, than in patients only treated with estrogen, mean percent increase 6.8%.

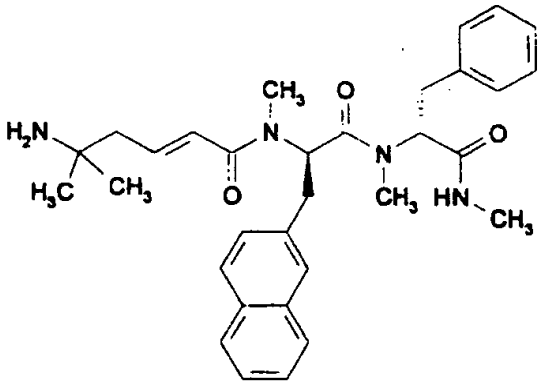
No beneficial effect was seen in patients who received GH plus placebo or placebo alone.

The effect on BMD hip showed exactly the same dose-response relationship as in spine with a greater increase in patients receiving the combined treatment compared to either estrogen or GH alone.

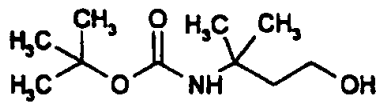
The following three examples illustrate preferred GH secretagogues.

EXAMPLE 3:

(2E) 5-Amino-5-methylhex-2-enoic acid N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)amide hydrochloride:



3-Hydroxy-1,1-dimethylpropylcarbamic acid tert-butyl ester:

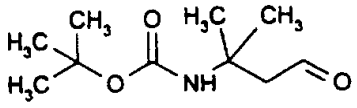


Step A: At 0 °C, ethyl chloroformat (1.10 mL, 11.5 mmol) was given dropwise t a solution of 3-tert-butoxycarbonylamino-3-methylbutanoic acid (2.50 g, 11.5 mmol) and triethylamine (1.92 mL, 13.8 mm l) in tetrahydrofuran (10 mL). The solution was stirred for 40 min at 0 °C. The

formed precipitate was filtered off and washed with tetrahydrofuran (20 mL). The liquid was immediately cooled to 0 °C. A 2M solution of lithium boronhydride in tetrahydrofuran (14.4 mL, 28.8 mmol) was added dropwise. The solution was stirred at 0 °C for 2 h, and then warmed to room temperature. over a period of 4 h. It was cooled to 0 °C. Methanol (5 mL) was added carefully. 1N Hydrochloric acid (100 mL) was added. The solution was extracted with ethyl acetate (2 x 100 mL, 3 x 50 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 mL) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was chromatographed on silica (110 g) with ethyl acetate/heptane 1:2 to give 1.84 g of 3-hydroxy-1,1-dimethylpropylcarbamic acid tert-butyl ester.

^{1}H-NMR ($CDCl_3$): d 1.33 (s, 6 H); 1.44 (s, 9 H); 1.88 (t, 2 H); 1.94 (br, 1 H); 3.75 (q, 2 H); 4.98 (br, 1 H).

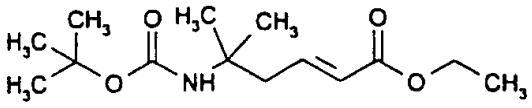
3-(tert-Butoxycarbonylamino)-3-methylbutanal:



Step B: DMSO (1.22 mL, 17.2 mmol) was added to a solution of oxalyl chloride (1.1 mL, 12.9 mmol) at -78 °C in dichloromethane (15 mL). The mixture was stirred for 15 min at -78 °C. A solution of 3-hydroxy-1,1-dimethylpropylcarbamic acid tert-butyl ester (1.75 g, 8.6 mmol) in dichloromethane (10 mL) was added dropwise over a period of 15 min. The solution was stirred at -78 °C for another 15 min. Triethylamine (6.0 mL, 43 mmol) was added. The solution was stirred at -78 °C for 5 min and then warmed to room temperature. The solution was diluted with dichloromethane (100 mL) and extracted with 1N hydrochloric acid (100 mL). The aqueous phase was extracted with dichloromethane (50 mL). The combined organic layers were washed with saturated sodium hydrogen carbonate solution (100 mL) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by column chromatography on silica (140 g) with ethyl acetate/heptane (1:3) to give 1.10 g of 3-(tert-butoxycarbonylamino)-3-methylbutanal.

MHz-^{1}H-NMR ($CDCl_3$): d 1.39 (s, 6 H); 1.45 (s, 9 H); 2.85 (d, 2 H); 4.73 (br. 1 H); 9.80 (t, 1 H).

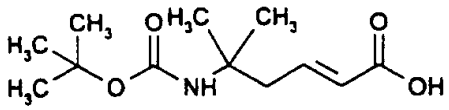
Ethyl (2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoate:



Step C: Triethylphoshonoacetate (1.96 mL, 9.8 mmol) was dissolved in tetrahydrofuran (30 mL). Potassium tert-butoxide (1.10 g, 9.8 mmol) was added. The solution was stirred for 40 min at room temperature. A solution of 3-(tert-butoxycarbonylamino)-3-methylbutanal (1.10 g, 5.5 mmol) in Tetrahydrofuran (6 mL) was added. The solution was stirred at room temperature. for 75 min. It was diluted with ethyl acetate (100 mL) and 1N hydrochloric acid (100 mL). The phases were separated. The aqueous phase was extracted with ethyl acetate (2 x 50 mL). The combined organic phases were washed with saturated sodium hydrogen carbonate solution (60 mL) and dried over magnesium sulfate. The solvent was removed in vacuo. The crude product was purified by column chromatography on silica (90 g) with ethyl acetate/hepatane (1:4) to give 1.27 g of ethyl (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoate.

^{1}H-NMR ($CDCl_3$): d 1.30 (s, 6 H); 1.30 (t, 3 H); 1.46 (s, 9 H); 2.62 (d, 2 H); 4.27 (q, 2 H); 4.42 (br, 1 H); 5.88 (d, 1 H); 6.94 (td, 1 H).

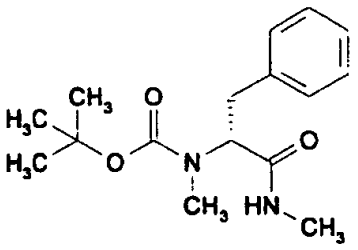
(2E)-5-(tert-Butoxycarbonylamino)-5-methylhex-2-enoic acid:



Step D: Ethyl (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoate (1.233 g, 4.54 mmol) was dissolved in dioxane (20 mL). Lithium hydroxide (0.120 g, 5.00 mmol) was added as a solid. Water (10 mL) was added, until a clear solution was reached. The solution was stirred 16 h at room temperature. The solution was diluted with water (70 mL) and was extracted with tert-butyl methyl ether (2 x 100 mL). The aqueous phase was acidified with 1N sodium hydrogensulfate solution (pH = 1) and was extracted with tert-butylmethylether (3 x 70 mL). The organic phases were combined and dried over magnesium sulfate. The solv nt was removed in vacuo to give 1.05 g of (2E)-5-(tert-butoxycarbonylamino)-5-methylhex-2-enoic acid. The crude product was used for further syntheses.

^{1}H-NMR (DMSO d_6): d 1.15 (s, 6 H); 1.35 (s, 9 H); 2.53 (d, 2 H); 5.75 (d, 1 H); 6.57 (br, 1 H); 6.75 (td, 1 H); 12.15 (s, 1 H).

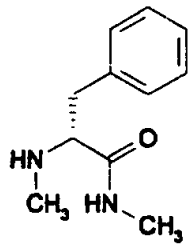
N-Methyl-N-((R)-1-(methylcarbamoyl)-2-phenylethyl)carbamic acid tert-butyl ester:



Step E: N-Tert-butoxycarbonyl-N-methyl-D-phenylalanine (1.22 g, 4.4 mmol), 1-hydroxybenzotriazole hydrate(0.59 g, 4.4 mmol) and 1-ethyl-3-(3-dimethyl-aminopropyl)carbodiimid hydrochloride (0.88 g, 4.6 mmol) were dissolved in N,N-dimethylformamide (25 mL) and stirred for 30 min. Methylamine (0.51 g of a 40% solution in methanol, 6.6 mmol) was added and the mixture was stirred overnight. Methylene chloride (80 mL) and water (100 mL) were added and the phases were separated. The organic phase was washed with sodium hydroxide (20 mL, 1N), sodium hydrogensulfate (50 mL, 10 %) and water (50 mL). The organic phase was dried (magnesium sulfate) and the solvent removed in vacuo to afford 1.39 g of N-methyl-N-((R)1-(methylcarbamoyl)-2-phenylethyl)carbamic acid tert-butyl ester.

^{1}H-NMR ($CDCl_3$): d 1.25, 1.35 (two s (br), 9H); 2.73-2.94 (m, 7H); 3.30-3.50 (m, 1H); 4.68, 4.90 (two m, 1H); 5.90, 6.12 (two s (br); 1H); 7.12-7.25 (m, 5H).

(R)-N-Methyl-2-methylamino-3-phenylpropionamide:

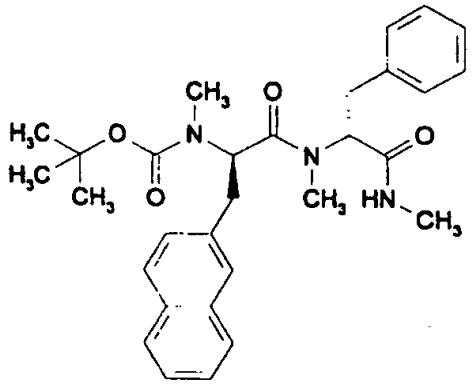


Step F: N-Methyl-N-((R)1-(methylcarbamoyl)-2-phenylethyl)carbamic acid tert-butyl ester (1.39 g, 7.23mmol) was dissolved in a mixture of trifluoroacetic acid (5 mL) and methylene chloride (10 mL) and stirred for 45 min. The volatiles were removed in vacu and the residue was

stirred with a mixture f thyl acetate (100 mL) and water (100 mL). Sodium hydrog n carbonate (50 mL, saturated) was added and the phases were separated. The organic phase was dried (magnesium sulfate) and the solvent removed in vacuo to afford 330 mg of (R)-N-methyl-2-methylamino-3-phenylpropionamide.

^{1}H-NMR ($CDCl_3$): d 2.1 (s(br), 3H); 2.32 (s, 3H); 2.77 (dd, 1H); 2.81 (two s, 3H); 3.21 (dd, 1H); 3.32 (dd, 1H); 7.12 (s(br), 1H); 7.20-7.34 (m, 5H).

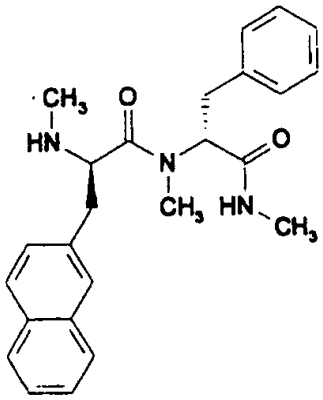
N-Methyl-N-{(1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl}carbamic acid tert-butyl ester:



Step G: (R)-Tert-butoxycarbonyl-N-methylamino-3-(2-naphthyl)propionic acid (548 mg, 1.66 mmol) was dissolved in methylene chloride (5 mL); 1-hydroxy-7-azabenzotriazole (227 mg, 1,66 mmol) was added along with N,N-dimethylformamide (2 mL). 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (351 mg, 1.83 mmol) was added and the solution was stirred for 15 min. (R)-N-Methyl-2-methylamino-3-phenylpropionamide (320 mg, 1.66 mmol) dissolved in methylene chloride (4 mL) and diisopropylethylamine (0.28 mL, 1.66 mmol) were added and the mixture was stirred overnight. Methylene chloride (50 mL) was added and the organic phase was washed with water (100 mL), sodium hydrogensulfate (50 mL, 5%) and sodium hydrogen carbonate (50 mL, saturated). The organic phase was dried (magnesium sulfate) and the solvent removed in vacuo. The residue was chromatographed (silica, 2 x 45 cm) using ethylacetate/methylene chloride (1:1) to afford 604 mg of N-methyl-N-{(1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-ph nylethyl)carbam yl)-2-(2-naphthyl)-ethyl}carbamic acid tert-butyl ester.

^{1}H-NMR ($CDCl_3$): d 1.05, 1.31, 1.56 (three s, 9H); 2.28-3.37 (several m, 13 H); 5.04, 5.17, 5.28, 5.48 (four dd, 2H); 7.05-7.79 (m, 12 H).

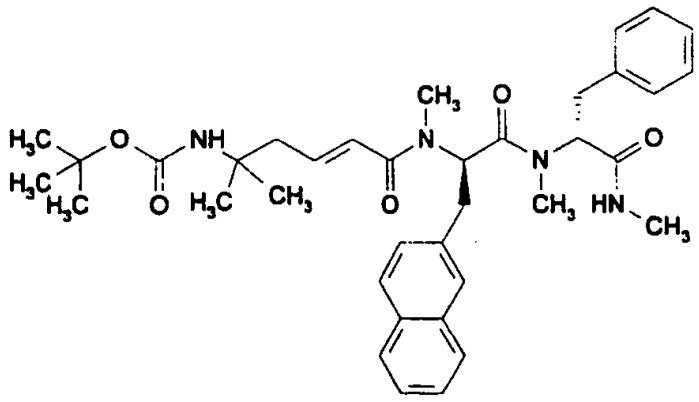
(2R)-N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide:



Step H: N-Methyl-N-{(1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl}carbamic acid tert-butyl ester (600 mg, 1.19 mmol) was stirred in trifluoroacetic acid/methylene chloride (1:1, 5 mL) for 10 min and the volatiles were removed in vacuo. The residue was stripped with diethylether (2 x 5 mL) and dissolved in methanol (2 mL) and mixed with sodium hydrogen carbonate (10 mL) and ethylacetate (15 mL). The organic phase was separated and dried (magnesium sulfate) to afford 420 mg of (2R)-N-methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide.

^{1}H-NMR ($CDCl_3$): (selected values) d 1.69 (s, 3H); 2.08 (d, 3H); 2.54 (s, 3H); 2.76 (dd, 1H); 2.92 (dd, 1H), 3.12 (dd, 1H), 3.31 (dd, 1H); 3.72 (dd, 1H), 4.95 (q (br), 1H); 5.50 (dd, 1H).

((3E)-1,1-Dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butyl ester:



Step I: (2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (200 mg, 0.82 mmol), 1-hydroxy-7-azabenzotriazole (112 mg, 0.82 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide hydrochloride (173 mg, 0.90 mmol) were dissolved in a mixture of methylene chloride (10 mL) and N,N-dimethylformamide (1 mL) and stirred for 15 min. N-Methyl-2-methylamino-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)-3-(2-naphthyl)propionamide (332 mg, 0.82 mol) dissolved in methylene chloride (5 mL) and diisopropylethylamine (0.14 mL) were added and the mixture was stirred overnight under nitrogen atmosphere. The mixture was diluted with methylene chloride (50 mL), washed with water (50 mL), sodium hydrogen carbonate (30 mL, saturated), and sodium hydrogensulfate (30 mL, 5%). The phases were separated and the organic phase was dried with magnesium sulfate and evaporated in vacuo. The residue was chromatographed (silica, 2 x 40 cm) to afford 450 mg of ((3E)-1,1-dimethyl-4-(N-methyl-N-((1R)-1-(N-methyl-N-((1R)-1-(methylcarbamoyl)-2-phenylethyl)carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)-carbamic acid tert-butyl ester.

^{1}H-NMR ($CDCl_3$): (selected values) d 1.20, 1.22, 1.24, 1.30, 1.41, 1.55 (six s, 15 H), 4.30, 4.40 (two s (br), 1H); 5.08, 5.18, 5.32, 5.60, 5.87 (five dd, 2H); 6.05 (dd, 1H); 6.75 (m, 1H).

Step J: ((3E)-1,1-Dimethyl-4-(methyl-((1R)-1-(methyl-((1R)-1-(methylcarbamoyl)-2-phenyl-ethyl)-carbamoyl)-2-(2-naphthyl)ethyl)carbamoyl)but-3-enyl)carbamic acid tert-butyl ester (403 mg, 0.63 mmol) was stirred in a mixture of trifluroacetic acdi (4mL) and methylene chloride (4 mL) for 10 min. The volatiles were removed in vacuo and the crude product was chromatograped on silica (400g) using a mixture of methylene chloride, ethanol and ammonia (25% in water) (80/18/2) as eluent. The isolated product was dissolved in 3M hydrochl ric acid in ethyl acetate and evaporated, then redissolved in methylene chloride and evaporated twice to afford 140 mg of the title compound.

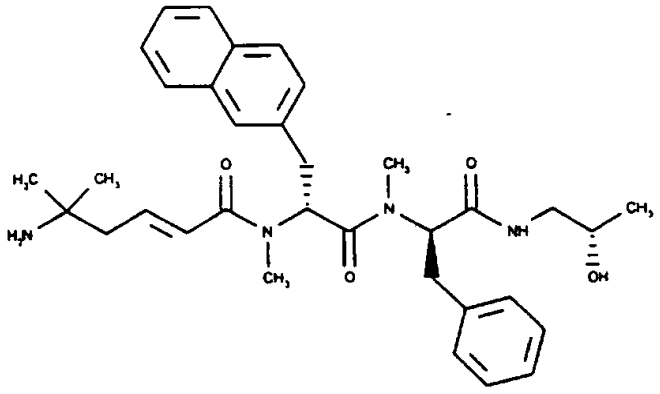
^{1}H-NMR ($CDCl_3$): d 1.05, 1.10, 1.15, 1.16 (four s, 6H); 2.07 (s (br); 3H); 5.12, 5.32, 5.40, 5.60, 5.91 (five dd, 2H); 6.05, 6.14 (two d, 1H); 6.80 (m, 1H)

HPLC: R_t = 29.02 min (Method A1)

ESMS: m/z = 529 (100%)$(M+H)^+$

EXAMPLE 4:

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-1-(((1R)-1-((2S)-2-hydroxypropylcarbamoyl)-2-phenylethyl)-methylcarbamoyl)-2-(2-naphthyl)ethyl)-N-methylamide:



This compound was prepared analogously to example 1. (S)-2-hydroxypropylamine was substituted for methylamine in step E.

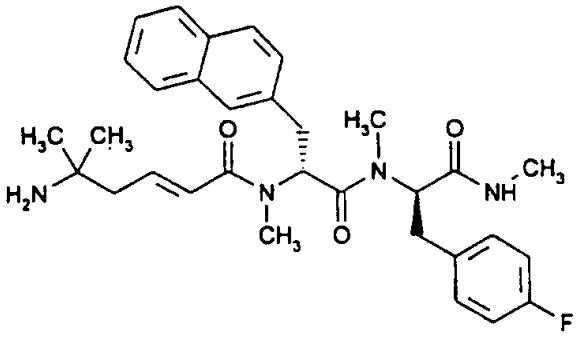
^{1}H-NMR ($CDCl_3$) (selected peaks, mixture of rotamers) d 3.90 (m, 1H); 5.55 (dd, 1H); 5.58 (d, 1H)

HPLC: R_t = 29.03 min (Method A1)

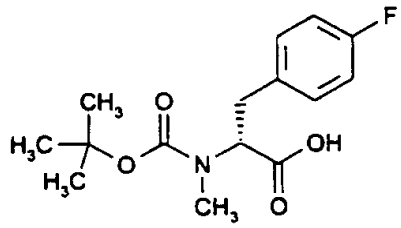
PDMS: m/z = 573.5 (100%)$(M+H)^+$

EXAMPLE 5:

(2E)-5-Amino-5-methylhex-2-enoic acid ((1R)-1-(((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylamide:



(R)-2-(N-tert-Butoxycarbonyl-N-methylamino)-3-(4-fluorophenyl)propionic acid:

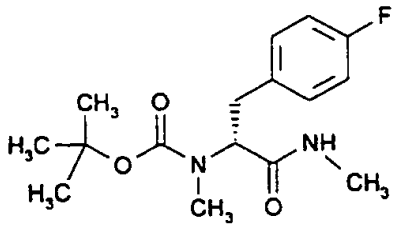


2-tert-Butoxycarbonylamino-3-(4-fluorophenyl)propionic acid (5.0 g; 17.7 mmol) was dissolved in dry tetrahydrofuran. Iodomethane (8.8 mL; 141 mmol) was added and the reaction mixture was cooled to 0° C. Sodium hydride (2.1 g; 53.0 mmol) was slowly added and the reaction mixture was stirred for 12 hours at room temperature. Ethyl acetate (50 mL) was added and water (20 mL) was added dropwise to the reaction mixture. The ethyl acetate was removed in vacuo and the residue was diluted with diethyl ether (30 mL) and water (100 mL). The organic phase was extracted with a saturated aqueous solution of sodium hydrogen carbonate (50 mL). Citric acid (5 %) was added to the combined aqueous phases until pH 3, which were then extracted with ethyl acetate (2 x 50 mL) and the phases were separated. The organic phase was washed with water (2 x 50 mL), an aqueous solution of sodium thiosulfate (5 %; 2 x 50 mL) and wat r (50 mL) and dried (magnesium sulfate). The solvent was remov d in vacuo and th residue was dissolved in diethyl ether (10 mL). Dicyclohexylamine (10 mL) was added.

Methylene chloride (30 mL) was added and the mixture was heated until the precipitate was dissolved. Diethyl ether (20 mL) and heptane (20 mL) were added and the reaction mixture was left 12 hours without stirring. The reaction mixture was filtered to afford 5.7 g of (R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-(4-fluorophenyl)propionic acid as a dicyclohexyl-ammonium salt.

^{1}H-NMR ($CDCl_3$) (mixture of rotamers) d : 1.21; 1.31 (two s, 9H); 2.75; 2.84 (two s, 3H); 2.86-3.02 (m, 1H); 3.28-3.42 (m, 1H); 4.65; 4.85 (two dd, 1H); 6.85-7.00 (m, 2H); 7.10-7.25 (m, 2H).

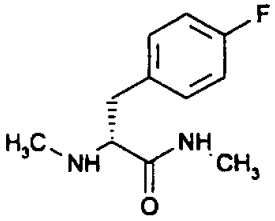
((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-methylcarbamic acid tert-butylester:



The dicyclohexylammoniumsalt of (R)-2-(N-tert-butoxycarbonyl-N-methylamino)-3-(4-fluoro-phenyl)propionic acid (3.00 g; 10.1 mmol) was dissolved in methylene chloride (30 mL) and washed with an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL). The organic phase was dried (magnesium sulfate) and filtered. 1-Hydroxybenzotriazole (1.40 g; 10.1 mmol) and N-(3-dimethylaminopropyl)-N´-ethylcarbodiimide hydrochloride (2.0 g; 10.6 mmol) were added to the filtrate and the reaction mixture was stirred for 15 min at room temperature. Methylamine (40 % in methanol; 0.75 g; 9.17 mmol) and diisopropylethylamine (1.7 mL; 10.1 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. The reaction mixture was washed with an aqueous solution of sodium hydrogen carbonate (sat; 50 mL) and an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (3 x 40 cm) using ethyl acetate/heptane (2:1) as eluent to afford 1.06 g of ((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)ethyl)-methylcarbamic acid tert-butylester.

^{1}H-NMR ($CDCl_3$) d : 1.29; 1.37 (two s, 9H); 2.74 (s, 3H); 2.8 (s, 3H); 2.82-2.95 (m, 1H); 3.36-3.48 (m, 1H); 4.63; 4.86 (m, 1H); 5.89; 6.14 (two s, 1H); 6.9-7.0 (m, 2H); 7.1-7.21 (m, 2H).

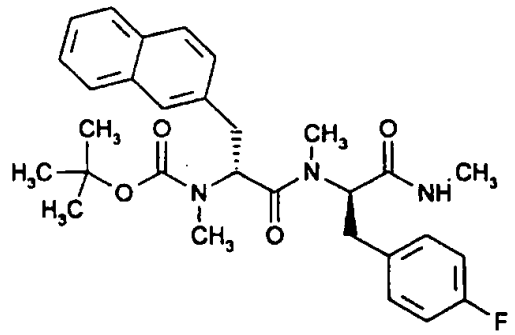
(2R)-3-(4-Fluorophenyl)-N-methyl-2-(methylamino)propion-amide:



((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-methylcarbamic acid tert-butylester (1.0 g; 3.22 mmol) was dissolved in methylene chloride (5 mL). Trifluoroacetic acid (5 mL) was added and the reaction mixture was stirred for 30 min at room temperature. Methylene chloride (30 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 30 mL) and sodium hydrogen carbonate (solid), were added to the reaction mixture, until pH 9. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.62 g of (2R)-3-(4-fluorophenyl)-N-methyl-2-methylaminopropionamide.

^{1}H-NMR ($CDCl_3$) d : 1.31 (s, 1H); 2.29 (s, 3H); 2.65-2.73 (m, 1H); 2.82 (d, 3H); 3.12-3.20 (m, 2H); 6.96-7.02 (m, 2H); 7.11 (s, 1H); 7.14-7.20 (m, 2H).

((1R)-1-(((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)methylcarbamoyl)-2-(2-naphthyl)-ethyl)methylcarbamic acid tert-butylester:

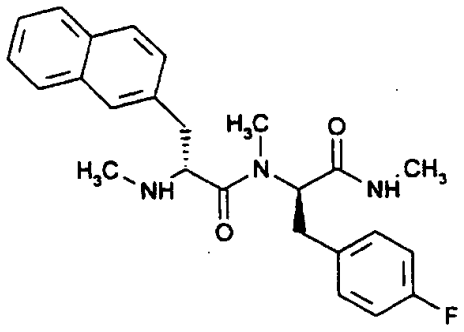


(2R)-2-(tert-Butoxycarbonylmethylamino)-3-(2-naphthyl)propionic acid (1.0 g; 3.1 mmol) was dissolved in methylene chlorid (20 mL). 1-Hydroxy-7-azabenzotriazole (0.43 g; 3.1 mmol) and N-(3-dimethylaminopropyl)-N´-ethylcarbodiimide hydrochlorid (0.63 g; 3.3 mmol) were added and the reaction mixture was stirred for 15 min at room temperature.

(2R)-3-(4-Fluorophenyl)-N-methyl-2-(methylamino)propionamide (0.6 g; 2.9 mmol) and diisopropylethylamine (0.54 mL; 3.1 mmol) was added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (30 mL) was added and the reaction mixture was washed with water (30 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 30 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 30 mL) and water (30 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (4.0 x 30 cm) using ethyl acetate/heptane (2:1) as eluent to afford 1.07 g of ((1R)-1-(((1R)-2-(4-fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylcarbamic acid tert-butylester.

^{1}H-NMR ($CDCl_3$) (selected peaks for major rotamer) d : 1.34 (s, 9H); 2.23 (d, 3H); 2.76 (s, 3H); 2.87 (s, 3H); 5.70 (dd, 1H); 5.95 (dd, 1H).

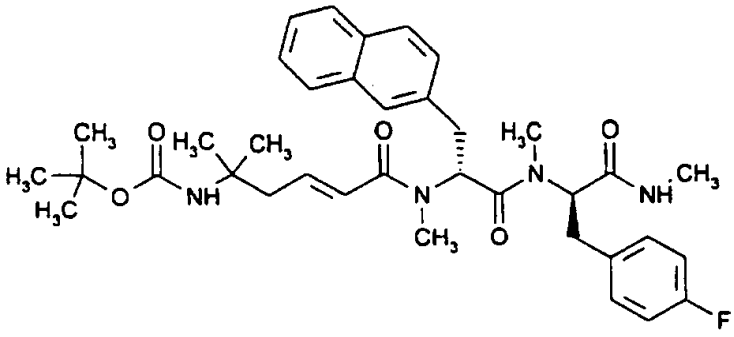
(2R)-N-((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)-ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide:



((1R)-1-(((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylcarbamic acid tert-butylester. (1.0 g; 1.92 mmol) was dissolved in methylene chloride (5 mL). Trifluoroacetic acid (5 mL) was added and the reaction mixture was stirred for 15 min at room temperature. Methylene chloride (25 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 25 mL) and sodium hydrogen carbonate (solid) was added to the reaction mixture until pH 8. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.75 g of (2R)-N-((1R)-2-(4-fluorophenyl)-1-methylcarbamoylethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide.

^{1}H-NMR ($CDCl_3$) d : 1.81 (s, 3H); 2.07 (d, 3H); 2.54 (s, 3H); 2.68-2.77 (m, 1H); 2.88-2.97 (m, 1H); 3.18 (dd, 1H); 3.27 (dd, 1H); 3.8 (dd, 1H); 4.95 (s, 1H); 5.43 (dd, 1H); 6.72 (t, 1H); 6.90 (t, 2H); 7.12 (dd, 2H); 7.32 (d, 1H); 7.42-7.50 (m, 2H); 7.62 (s, 1H); 7.70-7.83 (m, 2H).

(4(((1R)-1(((1R)-2(4-Fluorophenyl)-1-(methylcarbamoyl)-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester:



(2E)-5-(tert-Butyloxycarbonylamino)-5-methylhex-2-enoic acid (0.22 g; 0.89 mmol, prepared as in example 1) was dissolved in methylene chloride (10 mL). 1-Hydroxy-7-azabenzotriazole (0.13 g; 0.98 mmol) and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (0.2 g; 1.02 mmol) were added and the reaction mixture was stirred for 15 min at room temperature. (2R)-N-((1R)-2-(4-Fluorophenyl)-1-(methylcarbamoyl)ethyl)-N-methyl-2-methylamino-3-(2-naphthyl)propionamide (0.38 g; 0.89 mmol) and diisopropylethylamine (0.17 mL; 0.98 mmol) were added and the reaction mixture was stirred for 12 hours at room temperature. Methylene chloride (50 mL) was added and the reaction mixture was washed with water (50 mL), an aqueous solution of sodium hydrogen sulfate (10 %; 50 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 50 mL) and water (50 mL) and dried (magnesium sulfate). The solvent was removed in vacuo and the residue was chromatographed on silica (4 x 30 cm) using ethyl acetate/heptane (2:1) as eluent to afford 0.34 g of (4-(((1R)-1-(((1R)-2-(4-fluorophenyl)-1-methylcarbamoylethyl)methylcarbamoyl)-2-(2-naphthyl)-ethyl)methylcarbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butyl ester.

^{1}H-NMR ($CDCl_3$) (selected peaks for major rotamer) d : 0.85 (s, 3H); 0.87 (s, 3H); 1.42 (s, 9H); 2.12 (d, 3H); 2.72 (s, 3H); 2.96 (s, 3H); 5.75 (dd, 1H); 5,92 (dd, 1H); 6.12 (dd, 1H).

(4-(((1R)-1-(((1R)-2-(4-Fluorophenyl)-1-methylcarbamoyl-ethyl)methylcarbamoyl)-2-(2-naphthyl)ethyl)methyl-carbamoyl)-1,1-dimethylbut-3-enyl)carbamic acid tert-butylester (0.33 g;

0.51 mmol) was dissolved in methylene chloride (3 mL). Trifluoroacetic acid (3 mL) was added and the reaction mixture was stirred for 5 min at room temperature. Methylene chloride (25 mL), an aqueous solution of sodium hydrogen carbonate/sodium carbonate (pH 9; 25 mL) and sodium hydrogen carbonate (solid) were added to the reaction mixture until pH 9. The organic phase was dried (magnesium sulfate) and evaporated in vacuo to afford 0.18 g of the title compound.

^{1}H-NMR ($CDCl_3$) (selected peaks for major rotamer) d : 1.15 (s, 6H); 2.14 (d, 3H); 2.73 (s, 3H); 3.09 (s, 3H); 5.23 (dd, 1H); 5.90 (dd, 1H); 6.12 (dd, 1H).

PDMS: m/z 547.4 $(M+H)^+$

HPLC: R_t = 32.05 min

CLAIMS

1. A method of preventing or treating osteoporosis and related disorders, the method comprising cyclic administration, to an animal in need thereof, of a growth hormone component such as a growth hormone, a somatostatin antagonist or a growth hormone secretagogue in an amount sufficient to substantially prevent or reduce the degree of osteoporosis and/or to substantially increase bone strength.

2. A method according to claim 1, wherein the growth hormone component is administered for a period of from about 2 days to about 28 days at intervals from the termination of one period to the start of the next period of from about 1 week to about 26 weeks.

3. A method according to claim 2, wherein the growth hormone component is administered for a period of about 7 days at intervals from the start of one period to the start of the next period of about 6 weeks to about 12 weeks.

4. A method according to claim 1, wherein the animal is a mammal, in particular a human being.

5. A method according to claim 1, wherein the growth hormone component is human growth hormone.

6. A method according to claim 1, wherein a composition with anti-resorptive action on bone is continuously administered to the animal in addition to the cyclic administration of the growth hormone component.

7. A method according to claim 6, wherein said composition comprises an estrogen, in particular estradiol.

8. A method according to claim 6, wherein said composition comprises a compound with estrogenic effect.

9. A method according to claim 6, wherein said composition comprises one or more compounds selected from the group comprising Centchroman, Levormeloxifene, Raloxifene, Droloxifene, Tamoxifene, or Idoxifene.

10. A method according to claim 6, wherein said composition comprises a calcitonin.

11. A method according to claim 6, wherein said composition comprises a bisphosphonate.

12. A method according to any of the claims 7 to 11, wherein the composition comprises a combination of an estrogen and a gestagen.

13. A method according to any one of the preceding claims, wherein the dose or release of growth hormone is in the range of about 0.01-1 IU/kg body weight/day, in particular about 0.2 IU/kg body weight/day.

14. A method according to claim 6, wherein the dose of the composition with an anti-resorptive action on bone is in the range of from 0.001 to 10 mg/kg body weight/day and wherein the dose of growth hormone is in the range of about 0.01-1 IU/kg body weight/day, in particular about 0.2 IU/kg body weight/day.

15. Use of a growth hormone component for the manufacture of a medicament for the prevention or treatment of osteoporosis and related diseases, the medicament being intended for cyclic administration.

16. Use of a growth hormone component for the manufacture of a medicament for the prevention or treatment of osteoporosis and related diseases, the medicament being packaged with instructions for cyclic administration thereof.

17. Use of a growth hormone or a growth hormone component together with a composition with an anti-resorptive action on bone for the manufacture of a medicament for the prevention or treatment of osteoporosis and related diseases, the medicament being intended for cyclic administration of the growth hormone component and continuous administration of the anti-resorptive composition.

18. Use of a growth hormone component together with a composition with an anti-resorptive action on bone for the manufacture of a medicament for the prevention or treatment of osteoporosis and related diseases, the medicament being packaged with instructions for cyclic administration of the growth hormone component and continuous administration of the anti-resorptive composition.

19. Use of a growth hormone for the manufacture of a medicament for the prevention or treatment of osteoporosis and related diseases, the medicament being packaged with instructions for cyclic administration of the growth hormone component together with continuous administration of the anti-resorptive composition.

20. Use of a composition with an anti-resorptive action on bone for the manufacture of a medicament for the prevention or treatment of osteoporosis and related diseases, the medicament being intended for continuous administration over a period of time concomitantly with cyclic administration of a growth hormone component.

21. Products containing a) a growth hormone component and b) a compound with anti-resorptive effect on bone as a combined preparation for simultaneous, separate or sequential use in the prevention or treatment of osteoporosis.

22. A method according to claim 9, wherein said composition comprises Levormeloxifene or a structurally related compound thereof.

23. A method according to claim 9, wherein said composition comprises Levormeloxifene.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00239

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 38/27, A61K 31/56
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

WPI, TXTE, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	Calcif Tissue Int, Volume 40, 1987, John F. Aloia et al., "Coherence Treatment of Postmenopausal Osteoporosis with Growth Hormone and Calcitonin" page 253 - page 259	1-23
X	File 73:EMBASE, 9775990, Erdtsieck R.J. et al: "Treatment of post-menopausal osteoporosis with a combination of growth hormone and pamidronate: A placebo controlled trial", Clinical Endocrinology, 1995, 43/5 (557-565)	1-23
X	WO 9511029 A1 (MERCK & CO., INC.), 27 April 1995 (27.04.95), see page 45, second paragraph	21
A		1-8,10-20

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
19 Sept 1997	23 -09- 1997
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Carl-Olof Gustafsson Telephone No. +46 8 782 25 00

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/DK 97/00239

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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P,X	Clinical Endocrinology, Volume 46, 1997, Stefano Gonnelli et al., "Treatment of post-menopausal osteoporosis with recombinant human growth hormone and salmon calcitonin: a placebo controlled study" page 55 - page 61	1-23
X	EP 0436469 A1 (CIBA-GEIGY AG), 10 July 1991 (10.07.91), page 4, line 27 - page 5, line 6	21
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A	WO 9209304 A1 (RECKER, ROBERT, R.), 11 June 1992 (11.06.92)	1-23

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Information on patent family members

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PCT/DK 97/00239

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